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REVIEW

Elucidating the Role of Neutrophils in the Inflammatory Response to Behcet Syndrome

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Abstract: Behçet syndrome (BS) is a chronic, relapsing, multisystem inflammatory disorder in which both innate and adaptive immune mechanisms contribute to disease pathogenesis. Among innate immune cells, neutrophils have emerged as key effectors driving tissue inflammation, endothelial injury, and immunothrombosis. Early studies demonstrated enhanced chemotaxis, oxidative burst, and a primed activation state of circulating neutrophils, whereas more recent evidence highlights excessive neutrophil extracellular trap (NET) formation as an important contributor to vascular inflammation and thrombosis. In addition, recent omics-based studies have provided novel insights into neutrophil heterogeneity, activation pathways, and disease-specific signatures in BS. This review summarizes current knowledge on the role of neutrophils and NETs in the pathogenesis of BS, summarizes available evidence on mechanisms of neutrophil activation, and highlights potential directions for future research.

Keywords: Behçet syndrome, neutrophil, neutrophil extracellular traps, NET, oxidative burst, omics

Introduction

Behçet syndrome (BS) is a chronic, relapsing, multisystem inflammatory disorder characterized by recurrent oral and genital ulcers, cutaneous lesions including acneiform and erythema nodosum–like lesions, and articular, ocular, vascular, gastrointestinal, and central nervous system involvement. Although its pathogenesis has not been fully elucidated, both innate and adaptive immune systems are known to play important roles. Early immunological studies demonstrated exaggerated inflammatory responses in BS, particularly involving neutrophils, leading to the long-standing concept of a "hyperreactive" innate immune system.[1,2] However, despite decades of investigation, critical gaps remain in our understanding of the precise cellular and molecular mechanisms that initiate, amplify, and sustain inflammation across different disease phenotypes.

Among innate immune cells, neutrophils have emerged as a central effector population in BS. Early clinical observations, especially the pathergy phenomenon, suggested that minor trauma induces an excessive neutrophil-driven inflammatory response.[3,4] Experimental studies also confirmed that circulating neutrophils in BS display enhanced chemotaxis, increased oxidative burst, and a primed activation state even during clinically inactive disease.[1,2,5–9] More recent immunological studies have provided increasing evidence for the role of neutrophils, showing that they contribute to endothelial damage, immune-mediated thrombosis, abnormal cytokine and chemokine responses, and the formation of neutrophil extracellular traps (NETs), web-like chromatin structures released by activated neutrophils that contribute to inflammation and thrombosis when dysregulated.[9–12]

The aim of this review is to provide an up-to-date and comprehensive synthesis of the role of neutrophils in the pathogenesis of BS. We summarize both classical and recent studies including omics data on neutrophils in BS, and discuss therapeutic approaches targeting neutrophil-driven inflammation.

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Neutrophil Hyperactivation in Behçet's Syndrome

Neutrophil hyperactivation is characterized by enhanced chemotaxis and migration, increased oxidative burst, excessive degranulation, amplified inflammatory mediator release, and a primed state leading to exaggerated responses to secondary stimuli (Figure 1). Half a century ago, Matsumura et al reported increased ex vivo neutrophil chemotaxis in patients with BS compared with healthy controls (HCs) upon chemotactic stimulation.[1] Chajek-Shaul et al subsequently demonstrated higher neutrophil chemotaxis in HLA-B51 positive patients with BS compared with HLA-B51 negative patients and HCs.[5] Although these and other studies support enhanced neutrophil migration in BS, the findings have not been entirely consistent across different experimental settings. While ex vivo and in vitro assays frequently show increased neutrophil chemotaxis, in vivo studies using skin window techniques have reported variable results, including increased, normal, or reduced migration.[2,6,13–15] These differences are likely related to disease activity and to whether neutrophil migration is driven mainly by intrinsic neutrophil characteristics or by circulating plasma-derived factors. Overall, these findings suggest that increased neutrophil migration in BS is probably shaped by both intrinsic cellular properties and the inflammatory microenvironment.

Chronologic histopathologic studies of the pathergy reaction provide in vivo evidence for exaggerated neutrophil recruitment in BS. Ergun et al reported that neutrophil aggregates along the needle track could be detected as early as 4 hours after skin injury.[4] In contrast, Melikoglu et al showed that at 8 hours the proportions of neutrophils, lymphocytes, and monocytes were comparable between patients with BS and HCs, whereas by 48 hours a clear divergence emerged, with increased monocyte and lymphocyte infiltration in BS compared with HCs.[16] These temporal differences may reflect enhanced chemotactic recruitment of neutrophils in BS, which could be followed by prolonged tissue retention and

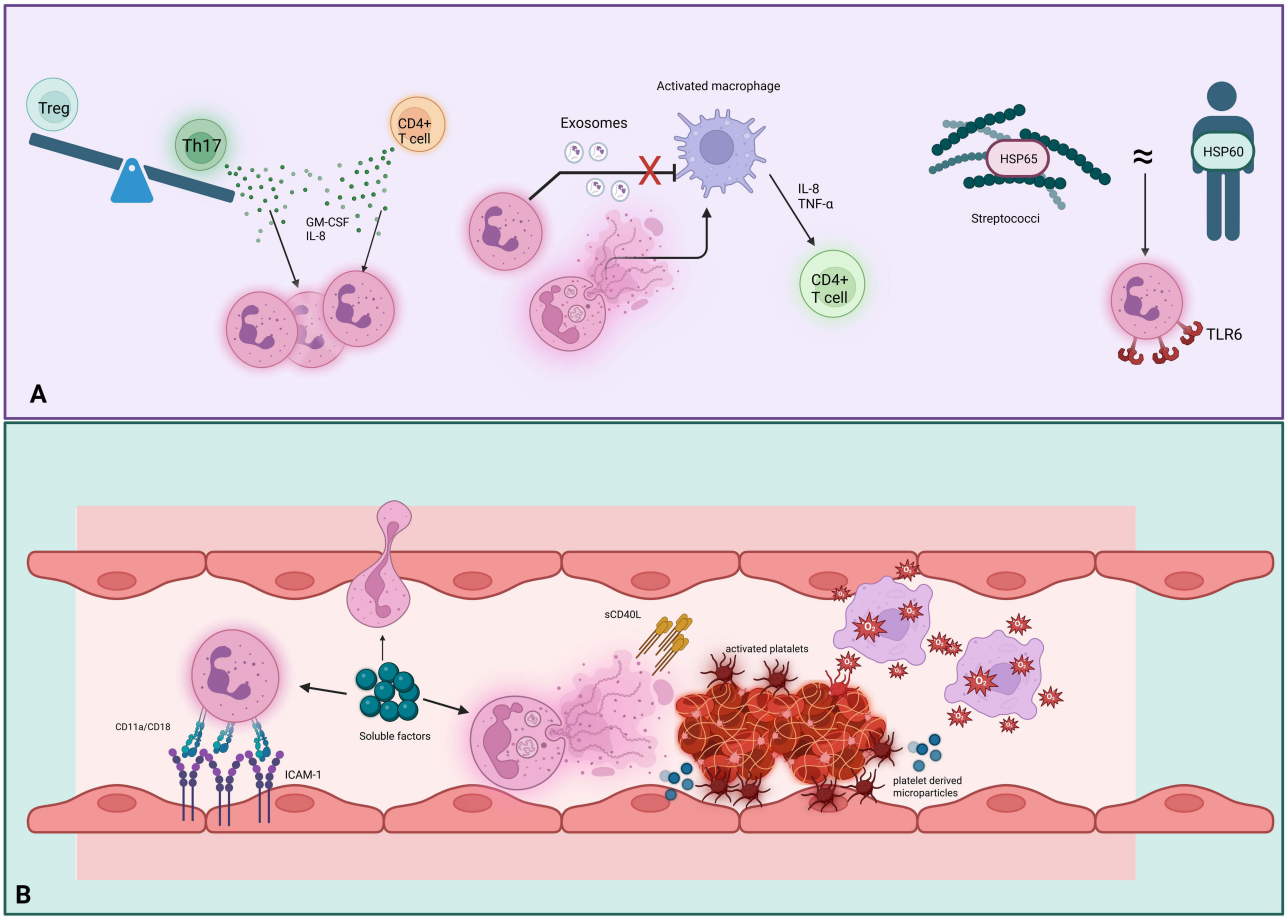


Figure 1 The role of neutrophils in the pathogenesis of Behçet syndrome. (**A**) Neutrophil-driven innate–adaptive immune crosstalk. (**B**) Neutrophil-mediated vascular inflammation and thromboinflammation, including endothelial adhesion, NET–platelet interactions, oxidative burst and thrombus formation.

amplification of inflammation, thereby contributing to defective resolution and persistent tissue inflammation. A recent study further suggests that the exaggerated pathergy response in BS is not solely driven by mechanical trauma but may also reflect heightened innate immune sensitivity to microbial-derived signals.[17] In this context, the association between BS and heat shock protein 60 (HSP-60) has long been recognized (Figure 1A). Indeed, molecular mimicry between microbial HSP-65 and human HSP-60 was first proposed as a pathogenic mechanism in BS, and subsequent studies demonstrated cross-reactive anti-HSP antibodies and HSP-derived epitopes capable of inducing T- and B-cell responses in affected patients.[18–22] Yavuz et al showed that neutrophils from patients with BS exhibit aberrant Toll-like receptor regulation, with exaggerated TLR-6–mediated responses upon stimulation with HSP-60 and Streptococcus sanguinis.[23] These findings suggest that neutrophils in BS may be primed to respond excessively to conserved microbial stress proteins. In line with this concept, a recent pathergy study demonstrated that addition of polysaccharide pneumococcal antigens markedly enhanced the pathergy reaction, particularly in active disease, and was associated with increased IL-1–related cytokine production.[17] Together, these observations suggest that the pathergy phenomenon in BS may not solely reflect a nonspecific inflammatory response to a skin trauma but could also involve altered neutrophil sensing of microbial and stress-related molecular patterns, potentially contributing to the amplification and persistence of local inflammation.

Emerging evidence further suggests that alterations in the gut and oral microbiota may act as additional stimulators of neutrophil hyperactivation in BS. Gut dysbiosis, characterized by a reduced abundance of short-chain fatty acid–producing bacteria, particularly butyrate-producing species, may impair immune regulation and promote a pro-inflammatory environment.[24] Experimental animal models have shown that transfer of microbiota from patients with BS is associated with increased neutrophil activation and enhanced Th1/Th17 responses.[25,26] In addition, alterations in the oral microbiota, particularly involving Streptococcus sanguinis, may contribute to neutrophil activation and NET formation through molecular mimicry mechanisms.[27]

Sahin et al investigated neutrophil–endothelial adhesion in BS in vitro, focusing on both cellular and circulating humoral factors.[28] Neutrophils from patients with BS show increased expression of adhesion molecules, particularly CD11a/CD18. Exposure of healthy neutrophils to BS serum induces a similar increase in adhesive capacity, highlighting the role of circulating plasma-derived factors. In addition, BS serum enhances endothelial activation, with increased ICAM-1 expression, especially under inflammatory conditions. Blocking the LFA-1–ICAM-1 interaction partially reduces neutrophil–endothelial adhesion, supporting the importance of this pathway (Figure 1B). They also reported that concentration of IL-8 was significantly higher in BS serum compared to HCs.

Phagocytic function of neutrophils in BS has been evaluated in several studies with inconsistent results. While some studies reported preserved phagocytic capacity comparable to HCs, others suggested altered phagocytic responses, particularly in patients with more severe disease manifestations.[8,29,30]

Oxidative burst is a key effector function of neutrophils and refers to the rapid production of reactive oxygen species (ROS) following cellular activation, which plays a central role in microbial killing but can also contribute to tissue and endothelial damage when dysregulated. Oxidative burst has been extensively investigated in BS; however, similar to neutrophil chemotaxis, the reported findings have been heterogeneous across studies. Early studies by Niwa et al reported that neutrophils from patients with active BS generate excessive oxygen radicals upon stimulation and induce endothelial cell damage when co-cultured with endothelial cells.[31] Subsequent study by Takeno et al demonstrated enhanced ROS production in neutrophils from patients with BS compared to HCs following fMLP stimulation.[7] They further reported higher ROS production in *HLA-B51* positive individuals irrespective of disease status, suggesting a possible association between *HLA-B51* and increased neutrophil oxidative responses in BS. Yoshida et al showed that serum from patients with BS markedly enhances superoxide production in normal neutrophils, indicating plasma-dependent neutrophil priming.[32] In contrast, Eksioglu-Demiralp et al reported reduced stimulation indices following fMLP and PMA activation, and proposed that neutrophils in BS are pre-activated or primed in vivo rather than constitutively hyperfunctional.[29] Notably, they did not observe any differences between *HLA-B51* positive and negative patients in contrast to Takeno et al More recently, Perazzio et al showed that neutrophil oxidative burst is not uniformly increased across all patients but is enhanced in those with severe disease and can be strongly induced by circulating plasma factors.[8]

To investigate the role of neutrophil-derived oxidative burst in BS, Becatti et al demonstrated that enhanced NADPH oxidase–dependent ROS production in neutrophils from patients with BS promotes fibrinogen oxidation (Figure 1B).

This oxidative modification resulted in altered fibrin structure and impaired fibrin polymerization. As a result, fibrin clots became more resistant to plasmin-mediated lysis, directly linking neutrophil oxidative stress to inflammation-induced thrombosis in BS.[10]

Neutrophil Extracellular Traps (NETs) and Thrombo-Inflammation in Behçet Syndrome

Neutrophil extracellular traps (NETs) are web-like structures composed of decondensed chromatin coated with histones and neutrophil-derived granular proteins, such as myeloperoxidase (MPO) and neutrophil elastase (NE). NET formation represents a distinct neutrophil effector mechanism that can trap and neutralize microorganisms independently of phagocytosis. However, excessive or dysregulated NET release has been increasingly recognized as a driver of sterile inflammation, endothelial injury, and thrombosis.[33]

Accumulating evidence suggests that enhanced NET formation contributes to key features in the pathogenesis of BS, particularly vascular inflammation and immunothrombosis (Figure 1A,B). The first direct evidence implicating NETs in the pathogenesis of BS was provided by Perazzio et al[9] They compared plasma samples from active and inactive BS patients and HCs and examined neutrophil and peripheral blood mononuclear cell (PBMC) activation. They demonstrated that neutrophils from patients with BS exhibited increased spontaneous NET release compared with HCs. This NET formation was further enhanced upon stimulation with BS plasma, with a more pronounced effect observed with plasma from patients with active disease, suggesting the involvement of plasma-derived soluble factors. Among several potential candidates, soluble CD40 ligand (sCD40L), a mediator involved in inflammatory and coagulation pathways, was markedly increased in both active and inactive patients with BS compared with HCs and patients with inactive systemic lupus erythematosus (SLE), and was also higher in patients with active BS than in those with active SLE. Finally, they showed that stimulation with recombinant sCD40L induced a similar effect on NET release, while blockade of sCD40L significantly reduced the NET-promoting effect of BS plasma.

Similarly, Safi et al showed that neutrophils from patients with active BS exhibited increased spontaneous NET formation and that plasma from patients with BS induced NET release in healthy neutrophils compared with samples from HCs.[11] They further showed that PAD4 expression, a key enzyme for NETosis, was increased both in neutrophils from patients with active BS and in healthy neutrophils upon stimulation with BS serum. Interestingly, they showed that spontaneous NET release from BS neutrophils was inhibited by colchicine, dexamethasone, a PAD4 inhibitor, and a ROS inhibitor, whereas BS serum-induced NET release was inhibited only by PAD4 or ROS inhibition. When NETs released from BS neutrophils were co-cultured with endothelial cells, increased endothelial apoptosis and cell death were observed. Finally, NETosis was predominantly detected in close proximity to affected blood vessels in biopsies of BS-associated vasculitis. Notably, in contrast to vascular and panniculitic lesions, NETs were rarely detected in biopsies of oral or genital ulcers, and previous data showed that saliva from patients with BS failed to induce NET formation in neutrophils.[34] Together, these findings suggest that NETosis in BS is not uniformly involved across all tissue manifestations but rather contributes selectively to specific lesions, particularly those with vascular involvement.

In line with the findings of previous studies, Le Joncour et al similarly demonstrated that neutrophils from patients with BS are prone to spontaneous NET formation and that markers of NETs are increased in patients with active disease.[12] In addition, they showed that circulating NET components, including cell-free DNA (cfDNA) and MPO–DNA complexes, were particularly elevated in patients with vascular involvement and were strongly associated with enhanced thrombin generation. Importantly, disruption of NET-derived DNA by DNase significantly reduced thrombin generation, and NETs were identified within inflamed vessels and thrombotic lesions, further supporting a direct link between NETosis, immunothrombosis, and vascular pathology in BS. Similarly, Kawakami et al identified NETs by immunohistochemistry in skin biopsies from three BS patients with biopsy-proven superficial venous thrombophlebitis associated with erythema nodosum–like lesions.[35]

Bettiol et al investigated the role of NETs in non-vascular manifestations of BS.[36] They demonstrated that NET levels were significantly increased in patients with active non-vascular BS compared with inactive disease and HCs. Notably, enhanced NET formation was particularly associated with mucosal, articular, and gastrointestinal involvement, whereas

no significant increase was observed in patients with isolated cutaneous, ocular, or neurological manifestations. In vitro experiments further showed that oxidative stress markedly enhanced NET release and neutrophil cell death, while colchicine effectively reduced NET formation and neutrophil damage independently of antioxidant effects. The authors suggested that NETosis may also contribute to tissue injury in non-vascular BS, although it should be noted that these observations were based on analyses of peripheral blood neutrophils rather than lesion-specific tissue samples.

In contrast to the findings of Bettiol et al, Wu et al demonstrated that NET formation is also markedly increased in ocular BS compared with HCs.[37] Using peripheral blood samples from patients with BS uveitis, they showed elevated serum markers of NETs, including double-stranded DNA and MPO, as well as increased expression of NETosis-related genes in neutrophils, accompanied by enhanced NET formation.

Li et al aimed to determine whether NETs actively promote autoinflammation by modulating innate-adaptive immune crosstalk, particularly through macrophage activation.[38] Consistent with previous studies, they confirmed that circulating NETs and neutrophil-derived NET formation, as well as serum and neutrophil ROS levels, were increased in patients with BS compared with HCs. Using NET-macrophage and macrophage-T cell co-culture systems, they demonstrated that NETs derived from BS neutrophils induce aberrant macrophage activation with enhanced IL-8 and TNF-α production and subsequently promote IFN-γ–producing $CD4^+$ T cell differentiation. They further showed that BS NETs were enriched in histone H4 and oxidized DNA, which may contribute to macrophage hyperactivation.

As NETosis analyses remain an evolving field without a gold-standard assay for assessing systemic NET formation, Bektas et al aimed to explore the utility of selected NETosis-related markers in BS and their associations with oral and systemic disease activity.[39] They included 30 patients with active BS and 10 HCs, and longitudinal serum and saliva samples were available from 18 patients during remission. Notably, NETosis markers were adjusted for neutrophil counts to minimize the confounding effect of neutrophilia during active disease. In unadjusted analyses, serum cfDNA and NE levels were higher in patients with active BS than in HCs. However, after adjustment for absolute neutrophil counts, these differences were no longer observed, and adjusted MPO and citrullinated histone H3 levels were lower in active disease. Salivary NETosis markers did not differ in cross-sectional analyses but salivary cfDNA decreased during remission in longitudinal follow-up. Overall, the authors suggested that circulating NETosis markers in BS are strongly influenced by neutrophil counts and that neutrophil-adjusted analyses are necessary to avoid overestimation of systemic NETosis, while salivary NET-related markers may provide additional information on local disease activity.

Omics Insights Into Neutrophils in Behçet Syndrome

While functional and clinical studies have established that neutrophils play an important role in the pathogenesis of BS, omics-based approaches have enabled a more comprehensive and unbiased characterization of neutrophil heterogeneity, activation states, and disease-specific signatures. Integrated omics technologies provide deeper insight into neutrophil-driven pathways that may not be captured by conventional methods.

Yu et al analyzed bulk RNA sequencing (RNA-seq) data from neutrophils of treatment-naïve patients with active BS with different types of organ involvement (n=10) and age- and sex-matched HCs (n=10).[40] Differentially expressed genes (DEGs) in BS patients were primarily enriched in chemokine, MAPK, Wnt, and NF-κB signaling pathways. To validate these findings, the authors subsequently recruited an independent cohort including patients with active BS (n=32), age- and sex-matched HCs (n=32), systemic lupus erythematosus (SLE; n=28), and antineutrophil cytoplasmic antibody–associated vasculitis (AAV; n=16). Chemotaxis-related genes, including *CCL5, CCR6*, and *ETS1*, were similarly expressed in BS, SLE, and AAV patients and were significantly overexpressed compared with HCs. Further subgroup analyses according to organ involvement in BS revealed that *CCL5* and *ETS1* expression was significantly higher in patients with vascular BS than in other BS subgroups.

Wang et al used single-cell RNA-seq (scRNA-seq) to define sex-specific heterogeneity of circulating neutrophils and to elucidate how distinct neutrophil subsets contribute to male-biased disease severity and poor prognosis in Behçet uveitis (BU).[41] They first identified five neutrophil clusters from 8 female and 8 male HCs. Conventional neutrophil clusters (clusters 0, 1, and 2), associated with inflammation ($S100P^+S100A12^+$), chemotaxis ($IL17RA^+CXCL8^+$), and ROS responses ($HBA1^+HBA2^+$), were enriched in males, whereas unconventional neutrophil clusters (clusters 3 and 4),

linked to regulation of T cell differentiation (*ANXA1*$^{+}$*IL7R*$^{+}$*CD52*$^{+}$) and interferon-α responses (*MX1*$^{+}$*IFIT1*$^{+}$*IFIT2*$^{+}$), were more abundant in females.

In BU patients, conventional inflammatory neutrophils were increased and ROS-responsive apoptotic neutrophils were reduced in both females and males compared with HCs, indicating a shared pro-inflammatory and apoptosis-resistant neutrophil phenotype. When female and male BU patients were compared, males (n=10) showed a further increase in conventional inflammatory neutrophils with enhanced inflammatory signaling, chemotaxis, and NET-related activity. In contrast, unconventional neutrophils with interferon-α responsiveness were markedly reduced and T cell–regulatory neutrophils were absent in male BU patients, whereas these unconventional neutrophil populations were preserved in female BU patients (n=8) under both homeostatic and disease conditions.

In functional experiments, male BU neutrophils displayed enhanced NET formation, increased IL-6 and TNF-α production, and reduced apoptosis, accompanied by more pronounced Th1/Th17 skewing and reduced Treg responses.

The same group next investigated whether the sex-specific differences observed at the transcriptional level are also reflected at the protein level by performing a proteomic analysis of circulating neutrophils in BU.[42] They analyzed neutrophils isolated from patients with active BU who had not received immunosuppressive treatment for at least one month (3F/6M) and from age- and sex-matched HCs (4F/5M). They demonstrated that neutrophils from BU patients exhibited a marked shift toward a pro-inflammatory and apoptosis-resistant phenotype, with increased expression of proteins involved in acute inflammatory responses, NET formation, and innate immune activation, alongside reduced expression of proteins related to apoptosis and metabolic pathways.

Notably, sex-specific differences were evident at the proteomic level. Neutrophils from male BU patients (n=6) showed enhanced activation of inflammatory pathways, including NET-associated and Fc receptor–mediated signaling, together with suppressed apoptotic programs. In contrast, neutrophils from female BU patients (n=3) were relatively enriched in proteins associated with cell adhesion and lipid metabolism, suggesting a more regulated or protective profile.

When the proteomic data were integrated with the transcriptomic data described above, these protein-level changes corresponded to distinct neutrophil subsets, with inflammatory neutrophil populations being more prominent and ROS-responsive, apoptosis-prone neutrophils being functionally impaired in male BU patients.

In another study, Wu et al compared circulating neutrophils from newly diagnosed, treatment-naïve BU patients (n=10) with those from age- and sex-matched HCs (n=10) using scRNA-seq.[37] They identified four distinct neutrophil subsets and demonstrated a marked enrichment of an S100A12^{+} neutrophil population in BU patients. This subset was characterized by enhanced maturation, increased ROS production, and a strong NET-forming capacity, indicating the predominance of a pro-inflammatory, NET-producing neutrophil phenotype in BU.

As discussed above, circulating plasma-derived factors play an important role in neutrophil activation in BS. Cai et al investigated whether plasma-derived exosomes contribute to neutrophil hyperactivation in BU.[43] They demonstrated that exosomes isolated from patients with active BU (n=6), but not from HCs (n=6), induced robust neutrophil activation, characterized by increased production of pro-inflammatory cytokines (IL-17 and IL-6) and chemokines (IL-8 and MCP-1), enhanced NET formation, and upregulation of NET-associated proteins (MPO and NE). Proteomic profiling of plasma exosomes revealed a marked reduction of SHP2, a key negative regulator of inflammatory signaling, in BU-derived exosomes (BU, n=10; HCs, n=10). Functional experiments further showed that knockdown of *PTPN11*, the gene encoding SHP2, in human neutrophil cell lines promoted neutrophil hyperactivation and NET release, whereas restoration of SHP2 attenuated these responses.

While Li et al[38] (discussed above) demonstrated that NETs actively drive macrophage hyperactivation and downstream Th1 polarization in BS, a more recent study has examined neutrophil–macrophage crosstalk from a distinct perspective by focusing on neutrophil-derived exosomes.[44] Active (n=39) and inactive (n=25) patients with BS and age-sex matched HCs (n=39) were included. They demonstrated that neutrophil-derived exosomes are quantitatively and qualitatively altered, with reduced miR-122-5p content, resulting in impaired suppression of macrophage activation and enhanced IRF5/TLR4-dependent inflammatory signaling in BS. Together, these findings suggest that neutrophil-macrophage crosstalk in BS may involve multiple, potentially complementary mechanisms. Further studies are required to clarify how these pathways interact and to define their relative contributions to disease pathogenesis.

Crosstalk Between Neutrophils, Platelets, and Other Immune Cells

Several studies have reported that platelets, particularly activated platelets, play a role in the pathogenesis of BS (Figure 1A).[45–47] Macey et al examined platelet and neutrophil activation in BS, focusing on the influence of age, sex, and disease activity.[48] They showed persistent platelet activation, reflected by increased P-selectin expression and platelet-derived microparticles, irrespective of clinical activity. Platelet microparticle levels varied with age, peaking in mid-adulthood and declining after the age of 50, whereas neutrophils exhibited chronically elevated CD11b expression across all subgroups, indicating sustained neutrophil priming. The authors suggested that age-related changes in platelet activation may influence platelet-neutrophil interactions over the course of the disease.

Keller et al described a prominent $CD4^{+}CXCL8^{+}CCR6^{+}$ T cell infiltrate in three neutrophil-dominated inflammatory diseases, including BS, pustular psoriasis, and generalized exanthematous pustulosis.[49] These cells were characterized by predominant production of CXCL8 and GM-CSF, with minimal expression of IL-5 and IFN-γ. This cytokine profile suggests that this T cell subset is distinct from classical Th1 and Th2 lineages and may be specialized in supporting neutrophil recruitment, activation, and persistence at sites of inflammation, thereby bridging adaptive immune responses with neutrophil-driven innate inflammation (Figure 1A).

IL-17–producing Th17 cells were discovered nearly two decades ago and have since been implicated in the pathogenesis of numerous autoimmune and inflammatory diseases. Th17 differentiation is initiated by IL-6 and TGF-β, enhanced by IL-1β and TNF- α, and IL-23 primarily promotes the expansion of already differentiated Th17 cells. Several studies in BS have suggested elevated IL-17 levels and a relative shift of the Th17/Treg balance toward Th17 dominance, collectively indicating that Th17-mediated immune responses are likely involved in the pathogenesis of BS.[50–53] Th17 cells can additionally promote neutrophil recruitment and activation through the production of GM-CSF and other proinflammatory cytokines (Figure 1A). On the other hand, clinical evidence regarding the role of the IL-17 pathway in BS remains inconsistent. A randomized controlled trial (RCT) demonstrated that the IL-17A inhibitor secukinumab was ineffective in Behçet's uveitis, and several case reports have described the emergence of de novo Behçet-like manifestations during secukinumab therapy administered for other indications.[54–57] These seemingly paradoxical findings may, at least in part, reflect the marked heterogeneity and plasticity of Th17 cells, which can adopt distinct functional states ranging from tissue-protective or homeostatic phenotypes to highly pro-inflammatory, pathogenic programs depending on environmental cues and cytokine signaling.[58] This functional diversity may also influence the extent and persistence of neutrophil-dominated inflammation in BS, potentially contributing to the heterogeneity of clinical manifestations and treatment responses.

Targeting Neutrophils for the Management of Behçet Syndrome

Based on the prominent role of neutrophils in the pathogenesis of BS drugs that target neutrophils rather than autoantibodies have been effectively used in this complex condition. Drugs that may decrease neutrophil counts by myelosuppression or immune-mediated mechanisms such as cyclophosphamide, methotrexate, and sulfasalazine, drugs that inhibit neutrophil migration, activation, or function such as colchicine and glucocorticoids, drugs that impair neutrophil oxidative killing such as dapsone, and drugs that indirectly suppress neutrophil activity such as TNF inhibitors, tocilizumab and secukinumab have been tried in the management of BS. It should be noted that affecting neutrophils is not the only mode of action for these drugs and we still do not know the exact mechanism for many of them.

Glucocorticoids

Glucocorticoids may modulate neutrophil-driven inflammation in BS through various mechanisms that suppress neutrophil effector function. One of these may be by activating the glucocorticoid receptor and inhibiting NF-κB– and AP-1–dependent transcription, which may cause reduced expression of pro-inflammatory cytokines, chemokines, and adhesion molecules critical for neutrophil recruitment to inflamed vascular and mucocutaneous tissues.[59] Functionally, glucocorticoids impair neutrophil chemotaxis, adhesion, and transendothelial migration, suppress the generation of reactive oxygen species and proteolytic enzymes, and attenuate endothelial–neutrophil interactions that contribute to vascular inflammation in BS, a disease where neutrophils are thought to be the main driver of inflammation-induced thrombosis.[60,61]

Despite the scarcity of RCT data, glucocorticoids are essential for the rapid suppression of inflammation in BS.[62] The induction treatment of life-threatening complications includes intravenous methylprednisolone pulses, usually given as 3 pulses on consecutive days for arterial involvement and up to 7–10 pulses for parenchymal nervous system involvement. This is followed by a daily dose of 1 mg/kg prednisolone, which is tapered over the following months. The starting dose for organ-threatening manifestations is usually 0.5–1 mg/kg prednisolone. The tapering schedule for all organ manifestations is tailored according to the response, which is carefully monitored through clinical, laboratory, and imaging findings. A low or moderate dose of glucocorticoids up to 20 mg/day may be given for a short time during acute exacerbations of arthritis or severe skin or mucosa manifestations. Chronic use of systemic glucocorticoids is not advised for mucocutaneous involvement. Intraarticular injections may be effective for acute arthritis and topical glucocorticoids can be used for active oral and genital ulcers, as well as for uveitis in addition to systemic therapy.[62]

Colchicine

Colchicine shows its anti-inflammatory effects mainly through modulation of neutrophil function, especially by disruption of microtubule assembly.[63] This results in inhibition of neutrophil chemotaxis and impairment of adhesion, mobilization, and recruitment to inflamed tissues, as well as suppression of neutrophil-derived superoxide production. Moreover, colchicine increases neutrophil-driven inflammatory amplification by inhibiting activation of the NLRP3 inflammasome, leading to reduced interleukin-1 beta processing and release.[63]

Colchicine has been the first-line treatment modality in BS patients who have skin, mucosa, and joint involvement without major organ involvement. There are 3 randomized controlled trials that assessed colchicine in patients with mucocutaneous involvement.[64–66] These showed good response rates for nodular lesions, genital ulcers, and arthritis, whereas 2 of the RCTs showed no efficacy for oral ulcers. Despite the controversial results on its benefit for oral ulcers, it is still the initial choice of treatment for BS patients with mucocutaneous and joint involvement due to its efficacy for reducing the frequency of skin manifestations and arthritis in majority of the patients and because it is cheaper and relatively safe compared to conventional or biologic immunosuppressives that can be used in these patients.[62]

Apremilast

Apremilast is a small molecule that specifically inhibits phosphodiesterase-4 (PDE4) and increases intracellular cyclic AMP levels, especially in immune cells effecting several inflammatory pathways and was shown to be effective on oral ulcers of BS.[67,68] A recent study exploring the effect of PDE4 inhibition in BS demonstrated that neutrophils from patients with BS showed increased activation, including elevated surface activation markers (CD64, CD66b, CD11b, CD11c), higher ROS production, enhanced NET formation, and a distinct transcriptomic signature enriched for innate immune, intracellular signaling, and chemotaxis pathways compared with healthy individuals.[69] They also showed that neutrophils infiltrating skin lesions in BS express PDE4 and inhibition of PDE4 with apremilast markedly reduced neutrophil activation in vitro by lowering surface activation markers, ROS generation, and NETosis. Moreover, similar dampening of neutrophil activation and associated gene expression was observed in patients treated with apremilast in vivo.

Apremilast significantly reduced the number and pain of oral ulcers compared to placebo, in 2 RCTs.[67,68] Patients had to have active oral ulcers, but no active major organ involvement. The Phase 3 trial included only patients who were active despite using at least one non-biologic medication for oral ulcers.[68] A pooled analysis of patients with genital ulcers at baseline in the Phase 2 and phase 3 trials showed significantly higher number of patients with complete remission of genital ulcers, compared to placebo. There was also significant improvement in overall disease activity, and patient reported outcomes including health-related quality of life in both RCTs.[67,68] These were followed by several real-life cohorts showing promising results for all mucocutaneous lesions and arthritis. The favorable safety profile is an advantage over immunosuppressive agents that can be used for mucocutaneous lesions.[70] Currently, apremilast is recommended as a second-line agent for patients with mucocutaneous involvement refractory to colchicine.[62]

Cyclophosphamide

Cyclophosphamide is an alkylating agent whose immunosuppressive effects are mediated through DNA crosslinking and inhibition of rapidly proliferating immune cells. Mature neutrophils are relatively resistant to direct cytotoxic effects of

cyclophosphamide, because they have a short lifespan and limited proliferative capacity, but cyclophosphamide seems to suppress neutrophil-mediated inflammation by its effects on the bone marrow myeloid progenitors and activated lymphocytes that drive neutrophil recruitment and activation.[71,72]

Cyclophosphamide used to be the main treatment option for BS patients with arterial aneurysms, thrombosis, intracardiac thrombosis and major venous involvement such as vena cava thrombosis or Budd-Chiari syndrome.[73] However, the risk of short and long-term adverse events including infertility and malignancies led to exploration of other options such as TNF inhibitors. A recent RCT comparing cyclophosphamide with infliximab among BS patients with vascular and nervous system involvement showed that infliximab provided higher complete remission rates with a complete remission definition that included clinical, laboratory, and imaging remission as well as glucocorticoid tapering.[74] The number of patients with mild to moderate adverse events were higher with cyclophosphamide, whereas the number of patients with serious adverse were similarly few with both drugs. A retrospective cohort of BS patients treated with cyclophosphamide suggested high infertility rates as well as infections and malignancies.[75] There is still room for cyclophosphamide for the management of vascular involvement in BS. A large single-center cohort of patients with vascular involvement who were treated with infliximab showed that cyclophosphamide may be effective in some patients who are refractory or intolerant to infliximab.[76] Adding cyclophosphamide to infliximab may also be an option for severe patients, but extreme caution is required due to the risk of infectious complications.

Biologic Agents

The main biologic agents used in the treatment of patients with BS comprise are TNF inhibitors, but a number of uncontrolled studies reported beneficial results with the use of other cytokine-targeted therapies including tocilizumab, ustekinumab, secukinumab, and guselkumab. While these drugs show their effect primarily through the inhibition of specific cytokines comprising IL-6, IL-17, IL-12, and IL-23, blocking these cytokines may indirectly help to control neutrophil-induced inflammation.

TNF inhibitors are unique for the treatment of BS since they provide high remission rates for all types of organs and system involvement. Moreover, they have become the first-line treatment option for patients with organ- or life-threatening disease. A recent multi-omics study integrating serum metabolomics, lipidomics, and peripheral immune-cell transcriptomics demonstrated that TNF inhibitors attenuate neutrophil hyperactivation in BS by downregulating TRPM2-mediated calcium signaling, thereby reducing NET formation and proinflammatory cytokine production.[77] Both monoclonal antibody TNF inhibitors and etanercept can be used for mucocutaneous and joint involvement. In fact, the first RCT with a TNF inhibitor in BS was conducted with etanercept and significantly lower number of oral ulcers, nodular lesions and papulopustular lesions was observed compared to placebo.[78] A more recent head-to-head trial comparing adalimumab with infliximab showed similar mucocutaneous response rates, whereas the overall response rate was higher and time to response was shorter with adalimumab.[79] In contrast to mucocutaneous and joint involvement, only monoclonal antibody TNF inhibitors are preferred in major organ involvement. A recent RCT with adalimumab showed better results compared to cyclosporine-A and no significant difference from interferon- α in the annualized relapse rates of uveitis.[80] Another RCT comparing infliximab with interferon- α showed similar benefit for uveitis with these agents.[81] The only RCT with a TNF inhibitor for vascular involvement was the study mentioned above that compared infliximab with cyclophosphamide.[74] Other than this, there are several open-label studies showing high response rates with especially infliximab for vascular, gastrointestinal, and nervous system involvement. Caution is required regarding infections, especially tuberculosis, in patients who use moderate or high dose glucocorticoids, concomitantly.

Interferon-α has been shown to be effective in RCTs and observational studies in patients with BS, particularly in refractory cases.[82] As discussed above, recent RCTs have reported efficacy comparable to TNF inhibitors in BS; however, its clinical use remains limited by restricted availability in many regions.[80,81] Interferon-α shows broad immunomodulatory effects on both innate and adaptive immune responses, although its precise mechanism of action in BS remains incompletely understood and is likely multifactorial. Available evidence suggests that these effects include in vivo normalization of activated immune cell subsets (NK cells and γδ T cells), ex vivo induction of IL-10 production and modulation of Th1/Th17 responses, as well as reduction of neutrophil adhesion.[83–85]

Two prospective observational uncontrolled studies with ustekinumab in patients with mucocutaneous and joint involvement showed good response rates, similar to what was observed in the active arm of the apremilast trial.[86,87] As already discussed above, secukinumab is not effective for uveitis,[54] and new BS cases with oral, genital, and gastrointestinal ulcers were reported during secukinumab use for other diseases,[55–57] but a small retrospective study of patients with mucocutaneous and joint involvement showed beneficial results.[88] Recently, a retrospective study with an IL-23 inhibitor, guselkumab reported promising results for mucocutaneous involvement.[89] Finally, tocilizumab was proposed as an alternative to TNF inhibitors for BU, especially for patients with dominant cystoid macular edema.[90] Interestingly, this agent may cause exacerbation of oral and genital ulcers.

Conclusion

Neutrophils play a central role in the inflammatory cascade of BS by linking innate immune activation with vascular injury, thrombosis, and adaptive immune dysregulation. Evidence from functional, clinical, and translational studies indicates that neutrophil hyperactivation and NET formation are important contributors to disease manifestations and therapeutic responses. Increasingly, effective treatments appear to exert part of their benefit through modulation of neutrophil-dependent pathways. Emerging omics data suggest that targeting neutrophil activation pathways, including NET formation and related signaling mechanisms, may represent potential therapeutic targets in BS; however, these approaches remain largely investigational. A clearer understanding of neutrophil-mediated mechanisms may therefore facilitate the development of more targeted and personalized therapeutic strategies for patients with BS.

Data Sharing Statement

Data sharing is not applicable to this review, as it does not involve the generation or analysis of new data.

Author Contributions

Yesim Ozguler: Conceptualization, Writing – original draft, Visualization, Writing – review & editing. Sinem Nihal Esatoglu: Conceptualization, Writing – original draft, Writing – review & editing. Gulen Hatemi: Writing – original draft, Writing – review & editing, Conceptualization, Supervision. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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